REMARKS

Status of the Claims

Pending claims

Claims 1 to 92 as filed are pending.

The Restriction Requirement and Election

The Patent Office alleged that the pending claims of the application as filed are directed to ten separate and distinct inventions under 35 U.S.C. §121.

In response to the Restriction Requirement, Applicants elected Group IV, claims 42 to 55, drawn to methods of generating a variant.

Claims amended, canceled and added in the instant amendment

Claims 1 to 41 and 56 to 92 are canceled, without prejudice, claims 42 to 55 are amended and new claims 93 to 106 are added. Thus, after entry of the instant amendment, claims 42 to 55 and 93 to 106 will be pending.

Outstanding Rejections

Claims 42 to 55 stand rejected under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Telephonic interview request

Applicants respectfully request a telephonic interview with the Examiner to discuss the issues raised in the first office action on the merits and the instant response and amendment.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for claims directed to methods using nucleic acids encoding amidases, wherein the nucleic acids have various lengths, can be found, *inter alia*, on page 40, paragraph [0132]. Support for claims directed to methods using nucleic acids encoding amidases, wherein the nucleic acids have various sequence identities to exemplary SEQ ID NO:1, can be found, *inter alia*, on page 11, paragraph [0047]. Support for claims directed to methods using polynucleotides capable of hybridizing under stringent conditions to a nucleic

acid having a sequence as set forth in SEQ ID NO:1, can be found, *inter alia*, on pages 12 to 13, paragraph [0050], and page 45, paragraph [0145].

Specification

Trademarks

The specification has been amended to capitalize trademarked products and processes. Names of manufacturers, such as Pharmacia or Promega, have not been capitalized.

Title

The title has been changed to better describe the elected, claimed invention.

Information Disclosure Statements

Applicants thank the Examiner for considering and initialing the Information Disclosure Statements of September 27, 2001, and November 6, 2002.

The reference listed as W70508 submitted in the IDS of November 6, 2002, is being resubmitted in a supplemental IDS with this response. Applicants note that this reference was first cited by the Examiner during prosecution of priority document USSN 09/609,570, now U.S. Patent No. 6,465,204.

Drawings

Corrected drawings are being submitted with this response.

Issues under 35 U.S.C. §112, second paragraph

Claims 42 to 55 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Applicants respectfully aver that the instant amendment addresses all of the issues raised in paragraphs 8 through 10, pages 4 to 6, of the instant office action.

Issues under 35 U.S.C. §112, first paragraph

Claims 42 to 55 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The address the issue of "any function" (see page 6, paragraph 12, of the office action) the claims have been amended to be directed to methods comprising generating variants of a genus of amidase-encoding nucleic acids.

The Patent Office alleged, inter alia, that the genus of polynucleotides used in the claimed methods is not sufficiently described in the specification because it is a large variable genus and a single species of that genus is insufficient to put one of skill in the art in possession of all of the attributes and features of all species of the genus (please note page 8, lines 10 to 13, end of paragraph 12, of the instant office action).

Applicants respectfully submit that the claimed invention is sufficiently described in the specification such that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully aver that a single species of a genus can be sufficient to put one of skill on the art in possession of all species with a claimed genus.

Applicants respectfully submit that only structurally and functionally related nucleic acids are encompassed by the scope of the claims. The nucleic acids of the claimed invention are described by structure (the exemplary sequence), a physico-chemical property (percent sequence identity and/or hybridization conditions) and function (amidase activity). All nucleic acids the genus (used in the claimed methods) must encode an enzyme having a percent sequence identity to an exemplary amidase coding sequence, or, hybridize under specific conditions to an exemplary amidase coding sequence. Applicants respectfully submit that describing a genus of polynucleotides in terms of physico-chemical properties (e.g., sequence identity or hybridization conditions) and function (e.g., encoding polypeptides having amidase activity) satisfies the written description requirement of section 112, first paragraph.

The Patent Office alleged that a single species of a genus is insufficient to put one of skill on the art in possession of all species within a claimed genus. However, Applicants respectfully aver that even a single species of the instant invention is sufficient to put one of skill on the art in possession of the claimed genus. There is no bright line rule that a single species of a genus is insufficient to put one of skill on the art in possession of all species with a claimed genus. Applicants respectfully refer to the USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph. In example 14 of the guidelines (a copy of which is attached as Exhibit A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example,

the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The Guidelines conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the genus of nucleic acids used in the claimed methods is described by structure (the exemplary nucleic acids or polypeptide sequences), a physico-chemical property (percent sequence identity or stringent hybridization conditions) and function (having an amidase activity). All nucleic acids of the genus used in the claimed methods must have a percent sequence identity to an exemplary sequence of the invention (or, hybridize under specific conditions to an exemplary sequence of the invention). The USPTO guidelines recognize that written description is met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity, hybridization under specific conditions) and a defined function (e.g., polymerase activity), the genus of claimed polypeptides also meet the written description requirements of section 112.

The genus of nucleic acids used in the claimed methods also fully complies with the requirements for written description of a genus of nucleic acids as set forth in University of California v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed. Cir. 1997). In Lilly, the Court stated that, "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs....*or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406.

As noted above, the instant claims clearly set forth specific structural and physical characteristics of the amidase-encoding nucleic acids. The claimed genus of nucleic acids all encode polypeptides having amidase activity and a specific physical characteristic, e.g., a % sequence identity to an exemplary nucleic acid, or, hybridization under specific conditions to an exemplary sequence of the invention. Therefore, the genus of nucleic acids used in the claimed

methods is defined via shared physical and structural properties in terms that "convey with reasonable clarity to those skilled in the art that Applicant, as of filing date sought, was in possession of invention." (Vas-Cath Inc. V. Mahukar, 19 USPQ2d 1111, (Fed Cir. 1991)).

More recently, the Federal Circuit stated

Similarly, in this court's most recent pronouncement, it noted:

> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)].

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the function of the amidases encoded by the nucleic acids used in the claimed methods is sufficiently correlated to a particular, known structure (the exemplary sequences) and a physical (physico-chemical) property (percent sequence identity or specific hybridization conditions). Accordingly, the sequences used in the claimed methods are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Applicants also respectfully refer to recently issued claims directed to genuses of polynucleotides based on sequence identity (and stringent hybridization) to an exemplary nucleic acid, see, e.g., recently issued claims directed to, e.g., 72.5% sequence identity, as in USPN 6,593,514 (July 15, 2003); 75% sequence identity (and "stringent hybridization"), as in USPN 6,586,215 (July 1, 2003); 80% sequence identity, as in USPN 6,680,185 (January 20, 2004), USPN 6,676,943 (January 13, 2004), USPN 6,677,145 (January 13, 2004), USPN 6,677,502 (January 13, 2004) and USPN 6,596,926 (July 22, 2003); 85% sequence identity, as in USPN 6,590,141 (July 8, 2003) and USPN 6,586,179; 86% sequence identity, as in USPN 6,583,337 (June 24, 2003); and, 90% sequence identity, as in USPN 6,689,352 (February 10, 2004) (see Exhibit B).

Accordingly, Applicants respectfully submit that the pending claims meet the

written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Enablement

Claims 42 to 55 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

The address the issue of "any function" (see page 9, lines 11 to 16, of the office action) the claims have been amended to be directed to methods comprising generating variants of a genus of amidase-encoding nucleic acids.

The Patent Office states that the specification is enabling for methods using the polynucleotide of SEQ ID NO:1, which encodes a polypeptide having amidase activity.

However, it is alleged, inter alia, that the specification does not provide reasonable enablement for the large number of amidase-encoding polynucleotides used in the claims methods. The Patent Office alleged that it is not routine experimentation to screen for multiple substitutions or multiple modifications as encompassed by the claims. It is alleged that it would have required some knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amidase activity to create variants of an exemplary nucleic acid and test them for the expression of polypeptides having amidase activity.

Applicants respectfully maintain that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, a genus of amidases to practice the claimed invention. As declared by Dr. Jay Short (see attached Rule 132 declaration), the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes such as amidases, and nucleic acids encoding amidases, was very high. As declared by Dr. Short, using the teaching of the specification, one skilled in the art could have selected routine methods known in the art at the time of the invention to express variants of nucleic acids encoding the exemplary enzyme of the invention and screen them for expression of polypeptides having amidase activity. Dr. Short declares that one skilled in the art could have used routine protocols known in the art at the time of the invention, including those described in the instant specification, to screen for nucleic acids encoding polypeptides having a percent sequence identity to SEQ ID NO:1, or active fragments thereof, for amidase activity. Dr. Short

declares that it was routine to screen for multiple substitutions or multiple modifications of an enzyme-encoding (e.g., amidase-encoding) sequence and predictably achieve positive results. As declared by Dr. Short, while the numbers of samples needed to be screened may have been high, the screening procedures were routine and successful results (i.e., finding variant nucleic acids encoding amidases) predictable.

Furthermore, Dr. Short declares that it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amidase activity to create variants of the exemplary nucleic acid and test them for the expression of polypeptides or peptides having amidase activity. Accordingly, it would not have taken undue experimentation to make and use the claimed invention, including identification of a genus of nucleic acids encoding amidases.

Whether large numbers of compositions (e.g., enzymes, antibodies, nucleic acids, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). In Hybritech, Inc., a single deposited antibody producing cell line enabled a claim generic to all IgM antibodies directed to a specific antigen. The Federal Circuit noted that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody specie was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large

numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of the biological sciences for the instant invention also recognize the need to screen numbers of negatives to find a sample that has the desired properties, e.g., amidase-encoding activity. Furthermore, as declared by Dr. Short, the screening procedures used to identify nucleic acids within the scope of the instant invention (e.g., identifying nucleic acids encoding amidases) were all well known in the art and at the time this application was filed. All were routine protocols for the skilled artisan. Thus, the skilled artisan using Applicants' written disclosure could practice the instant claimed invention without undue experimentation.

Accordingly, Applicants respectfully submit that the pending claims meet the written description and enablement requirements under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

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CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to **Deposit Account No. 03-1952**, ref Attorney Docket No. **564462000420**. Please credit any overpayment to this account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858 720 5133.

Respectfully submitted,

Date: Feb. 12, 2004

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